

Kinetic influences on enantioselectivity in asymmetric catalytic hydrogenation¹

Yongkui Sun^a, Jian Wang^a, Carl LeBlond^a, Ralph N. Landau^{a,2},
Joseph Laquidara^b, John R. Sowa Jr.^b, Donna G. Blackmond^{a,*},³

^a Merck and Co., Inc., P.O. Box 2000 RY55-228, Rahway, NJ 07065, USA

^b Department of Chemistry, Seton Hall University, South Orange, NJ 07079, USA

Abstract

Examples from both homogeneous and heterogeneous catalytic systems are presented which demonstrate the role that reaction dynamics may play in dictating the ultimate enantioselectivity observed in asymmetric hydrogenation reactions. The hydrogenation of allylic alcohols using Ru(*S*)-binap and the hydrogenation of α -keto esters using cinchona-modified supported Pt are discussed. This work highlights the importance of considering reaction kinetics in addition to the stereochemical aspects of the chiral catalytic environment in interpreting catalytic behavior in asymmetric hydrogenation reactions.

1. Introduction

Asymmetric catalysis offers an efficient synthetic route to optically pure substances in which a catalyst serves as a source for the multiplication of chirality. Significant advances in the synthesis of new chiral ligands have led to several important commercial processes in homogeneous asymmetric catalysis. These include the pioneering work which led to the process for L-DOPA manufacture [1] and the development of the (binap) ligand which plays an important role in the largest current commercial asymmet-

ric catalytic process, the production of (*S*)-menthol [2]. By contrast, heterogeneous asymmetric catalysis is still in its infancy, with high enantioselective efficiency being reported for only a relatively few catalytic systems and a much narrower range of organic substrates [3].

In studies of both homogeneous and heterogeneous asymmetric catalytic hydrogenation, rationalization of observed enantioselectivities has in most cases focused on understanding the nature of the chiral environment of the catalyst. Characterization of the stereochemistry of new chiral ligands for organometallic molecules receives much attention in homogeneous asymmetric catalytic systems. In heterogeneous catalysis, investigations have attempted to correlate the chiral efficiency of modified metal surfaces with metal particle size, structure, and other catalyst characteristics. As Noyori has recently pointed out [4], however, chiral catalysis is in

* Corresponding author.

¹ Communication presented at the First Francqui Colloquium, Brussels, 19–20 February 1996.

² Present address: Sandoz Pharmaceutical Corporation, 59 Route 10, East Hanover, NJ 07936-1080, USA.

³ Present address: Max-Planck-Institut für Kohlenforschung, D-45470 Mülheim-an-der-Ruhr, Germany.

fact *four*-dimensional chemistry, and the stereochemical aspects of chiral catalysts must be combined with an understanding of the role that reaction dynamics may play in determining enantioselectivity. This paper presents one example each from both homogeneous and heterogeneous catalysis in which the monitoring of reaction progress was found to be of paramount importance in rationalizing the ultimate enantioselectivity achieved in the reaction.

2. Experimental

Details of the experiments described in this paper are given elsewhere [5–9]. The homogeneous catalytic reaction of geraniol (Alfa, 99%) in methanol (Aldrich, 99.9%) was carried out over $[\text{RuCl}_2(\text{S})\text{-tolyl-binap}]_2 \cdot \text{NEt}_3$ (Strem) at 283 K and 500 kPa using a substrate/Ru ratio of 1400 mol/mol [5]. The heterogeneous catalytic hydrogenation of ethyl pyruvate (Aldrich, 98%) was carried out as described previously [6–9] with a cinchona alkaloid-modified 1 wt% Pt/ Al_2O_3 (Precious Metals Corporation) catalyst using a variety of reaction conditions as presented in Table 1.

Hydrogenation reactions were carried out in a reaction calorimeter (Mettler RC1). Reaction rates were measured by monitoring the calibrated heat flow of the reaction as described previously [10]. Automated data acquisition at

six-second intervals with an accuracy of better than 0.1 W afforded an extremely accurate measurement of reaction rate throughout the reaction. Briefly, Eq. (1) shows that for an isothermal, batch reacting system, the heat flow is proportional to the reaction rate:

$$q_r = V_r \sum_i \Delta H_{\text{rxn},i} \left(\frac{dC_i}{dt} \right) \quad (1)$$

where q_r is the heat released or consumed by the reaction, V_r is the volume of the reactor contents, (dC_i/dt) is the reaction rate and $\Delta H_{\text{rxn},i}$ the heat of reaction of the i th reaction. Integration of the heat flow curve provides the overall heat of reaction. The fractional heat evolution (FHE) at any point in the reaction may be used as a measure of the conversion of substrate:

$$\% \text{ conversion} = \text{FHE} = \frac{\int_0^t q_r(t) dt}{\int_0^{t_r} q_r(t) dt} \quad (2)$$

Product selectivity, reported as absolute enantiomeric excess, was measured for both systems by GC on a Chiraldex B-TA chiral column:

$$\% \text{ ee} = \frac{|[R] - [S]|}{[R] + [S]} * 100 \quad (3)$$

Enantiomeric excess defined in this way is an integral property of the batch reaction, and may also be called cumulative %ee to distinguish it

Table 1

Reaction parameters for the asymmetric hydrogenation of ethyl pyruvate 1 wt% Pt/ Al_2O_3 catalyst at 580 kPa

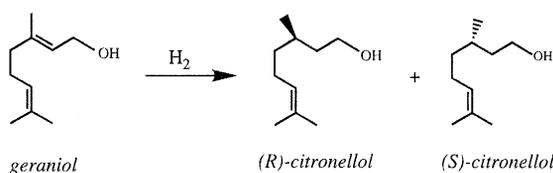
Symbol (see Fig. 6)	Temperature (K)	Substrate concentration (M)	Modifier concentration (mg/l)	Modifier	Solvent	Catalyst pre-reduction
▽	263	1	100	dihydrocinchonidine	1-propanol	no
□	283	1	100	dihydrocinchonidine	1-propanol	no
▷	283	0.5	100	dihydrocinchonidine	1-propanol	no
+	283	0.25	100	dihydrocinchonidine	1-propanol	no
*	283	1	100	dihydrocinchonidine	1-propanol	yes
●	283	1	100	dihydrocinchonidine	methylacetate	no
×	303	1	100	dihydrocinchonidine	1-propanol	no
○	303	1	100	cinchonidine	1-propanol	no
△	303	1	10	dihydrocinchonidine	1-propanol	no
◇	303	1	1000	dihydrocinchonidine	1-propanol	no
◁	323	1	100	dihydrocinchonidine	1-propanol	no

from a second property, incremental %ee, which is defined as the %ee for the product formed in the interval between two consecutive analytical data points at times t_{i-1} and t_i .

3. Results and discussion

3.1. Hydrogenation of geraniol with $[\text{RuCl}_2(\text{S})\text{-tolyl-binap}]_2 \cdot \text{NEt}_3$

Enantioselective hydrogenation of allylic alcohols such as geraniol has been extensively studied by Noyori [11] using homogeneous Ru(binap) catalysts:



As in many asymmetric catalytic reactions, enantioselectivity has been found to be strongly pressure dependent. For hydrogenation of geraniol using a Ru-(*S*)-binap catalyst, the enantioselectivity to (*R*)-citronellol increased from 70 to 98% as the reaction pressure was increased from 4 to 100 atm (400–10,000 kPa).

In our studies of this system, we observed a marked shift in enantioselectivity over the course of a single, constant pressure reaction [5]. Enantioselectivity of the batch reaction mixture, which at 10% conversion was ca. 85%ee to (*S*)-citronellol, rose to over 40%ee to (*R*)-citronellol at high conversion. This intriguing inversion in enantioselectivity was accompanied by unusual reaction rate behavior, as shown in Fig. 1. Two distinct rate regimes were observed, with a significantly faster rate process followed by a much slower one. These two rate regimes correspond to two distinct regions of almost opposite enantioselectivity, as shown in Fig. 2.

Detailed analysis of the reaction mixture revealed that the substrate geraniol underwent a

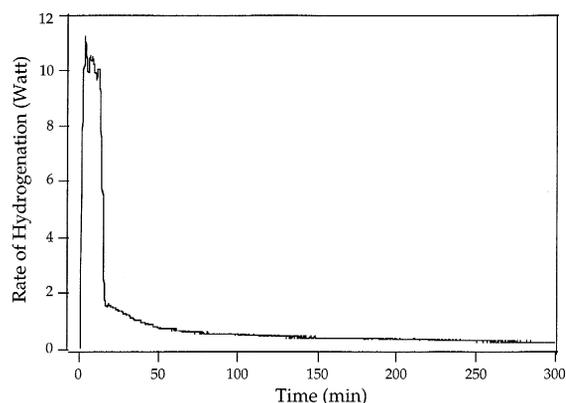


Fig. 1. Rate of hydrogenation of geraniol with $[\text{RuCl}_2(\text{S})\text{-tolyl-binap}]_2 \cdot \text{N}(\text{C}_2\text{H}_5)_3$ at 293 K and 500 kPa.

highly stereoselective isomerization to a terminal olefin, γ -geraniol, in the initial reaction mixture with the Ru(binap) catalyst under Ar. Studies of the isomerization equilibrium reaction showed that approximately 20% γ -geraniol was formed at 318 K (Fig. 3). Upon exposure to hydrogen, these two prochiral isomeric olefins reacted at significantly different rates with respectively high enantioselectivities to β -citronellol products of opposite absolute stereochemistry. Fig. 4 shows that the (*S*)-citronellol product was produced rapidly in the beginning of the reaction from the γ -geraniol substrate, followed by production of increasing amounts of the (*R*)-citronellol product which formed more slowly from geraniol after consumption of the γ -geraniol.

NMR evidence suggests that this isomerization reaction is not suppressed under hydrogen [12]. Hydrogenation of the terminal isomer occurs so rapidly that direct observation of its formation is impossible under standard conditions of the hydrogenation reaction.

Scheme 1 summarizes the findings of these experiments. The hydrogenation of geraniol to (*R*)- and (*S*)-citronellol is part of a complex reaction network in which ultimate enantioselectivity is determined by the relative rates of the isomerization and hydrogenation reactions.

The presence of this isomerization pathway offers a possible explanation for the observed

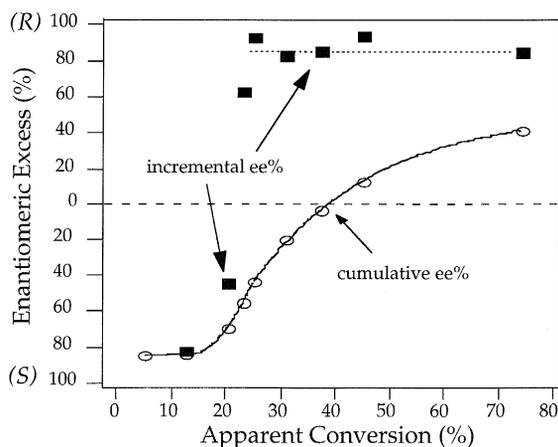


Fig. 2. Incremental and cumulative enantiomeric excess as a function of geraniol conversion in the hydrogenation of geraniol with $[\text{RuCl}_2(\text{S-tolyl-binap})_2 \cdot \text{N}(\text{C}_2\text{H}_5)_3]$ at 293 K and 500 kPa.

effects of hydrogen pressure on enantioselectivity in this system. The increased driving force for hydrogenation at high hydrogen pressure may increase the geraniol hydrogenation rate relative to its isomerization rate, resulting in a higher concentration of (*R*)-citronellol product and hence high enantioselectivity. At low pressure, the hydrogenation of geraniol may proceed slowly enough to allow a significant contribution through the isomerization pathway to γ -geraniol, with its concomitant hydrogenation to give primarily (*S*)-citronellol. The importance

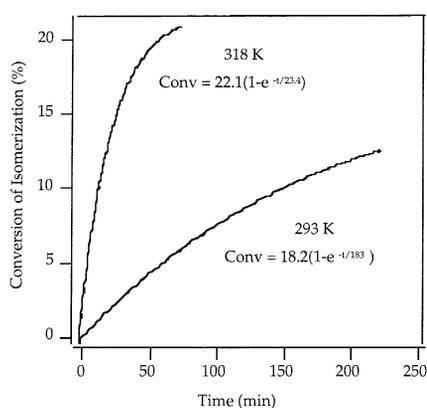


Fig. 3. Temperature dependence and activation energies for the isomerization reaction between geraniol and γ -geraniol between 293 and 318 K.

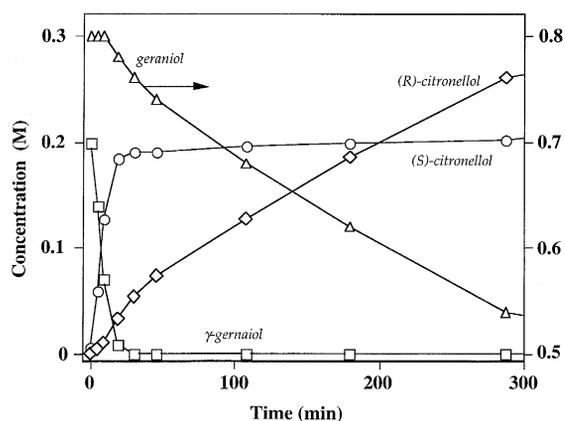
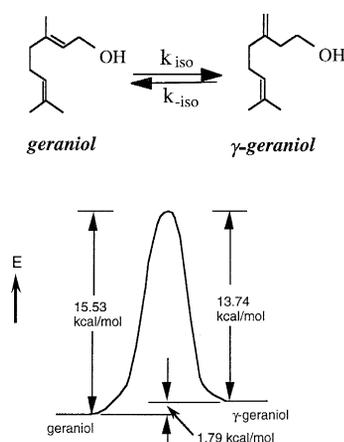
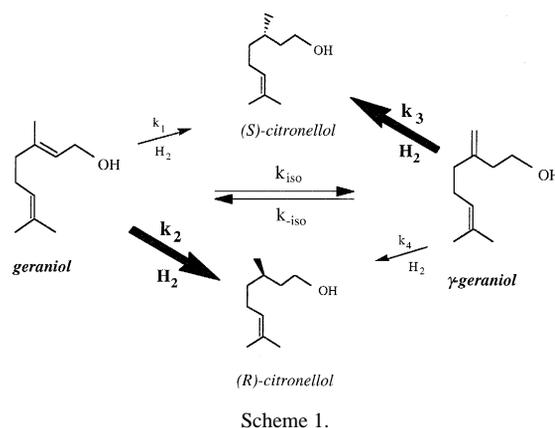


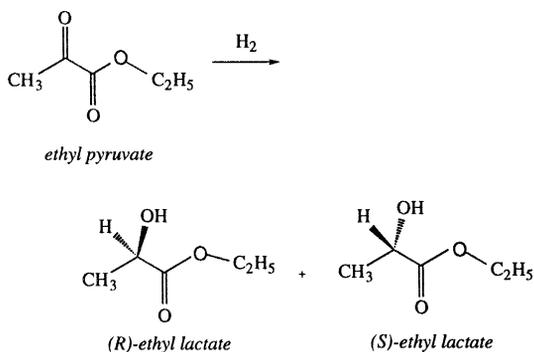
Fig. 4. Concentration of reactant and product species as a function of reaction time in the hydrogenation of geraniol and its isomer γ -geraniol to form (*R*)- and (*S*)-citronellol with $[\text{RuCl}_2(\text{S-tolyl-binap})_2 \cdot \text{N}(\text{C}_2\text{H}_5)_3]$ at 293 K and 500 kPa.



of reaction dynamics is thus highlighted by this case in which coupling between reactions in a series–parallel network is shown to exert a dramatic influence on enantioselectivity.

3.2. Hydrogenation of ethyl pyruvate with cinchonidine-modified Pt

Enantioselectivity in the hydrogenation of α -keto esters to α -hydroxy esters using heterogeneous Pt catalysts has been reported to be affected by a number of variables including hydrogen pressure, solvent, metal particle size and structure, and type of support. The hydrogenation of ethyl pyruvate to (*R*)- and (*S*)-ethyl lactate using cinchonidine-modified Pt/Al₂O₃ catalysts is the most commonly studied system [3]:



Investigations of the kinetics of this reaction have been presented ([8,13]), and the influence of other rate processes such as various diffusion steps has been discussed [7,9,14]. One interesting phenomenon, first noted by Wells and coworkers [15], is the presence of a transient period of rising reaction rate and enantioselectivity in the early stages of the reaction. This is shown in Fig. 5 where the reaction rate (determined by heat flow measurements), substrate conversion, and product enantioselectivity (determined from analytical sampling), are plotted over the course of the reaction at 283 K (see Table 1). The striking increase in rate reached a peak near 20% conversion, concomitant with

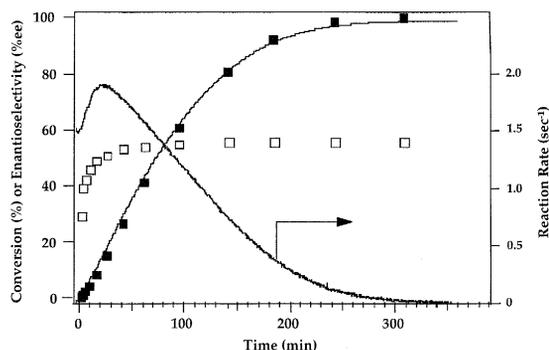


Fig. 5. Enantiomeric excess (open symbols), conversion (filled symbols), and reaction rate as a function of reaction time in the hydrogenation of ethyl pyruvate using cinchona-modified Pt/Al₂O₃ at 283 K and 580 kPa.

the establishment of steady-state enantioselectivity.

The significant changes in both rate and enantioselectivity that occur during this induction period require that great care be taken in studies where initial rate measurements are used in reporting catalytic data, posing a challenge for accurate experimental measurement. Since the heat flow of a reaction is directly proportional to its rate, reaction calorimetry offers a dramatic means of monitoring this unusual rate behavior which is difficult to observe by other methods. An interesting point to note is that the solid line representing conversion in Fig. 1 were determined not from a curve fit of the data points obtained from analytical sampling, but from integration of the heat flow data to give fractional heat evolution over the course of the reaction (as described in Section 2). This close agreement between two independent measures of extent of reaction, the calorimetric data and the data obtained from analytical sampling, demonstrates that the combination of techniques provides a sensitive means of monitoring both reaction rate and enantioselectivity over the entire course of the reaction, a critical concern in such a case where the reactive behavior changes dramatically as the reaction progresses.

Investigations of this induction period in rate and enantioselectivity were carried out over a

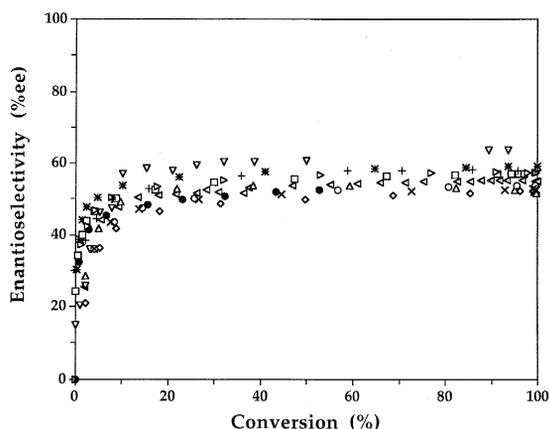


Fig. 6. Enantiomeric excess as a function of conversion of substrate in the hydrogenation of ethyl pyruvate using cinchona-modified Pt/Al₂O₃ over a range of reaction conditions (see Table 1 for an explanation of reaction conditions).

wide range of reaction conditions, as shown in Table 1. The results of these investigations are shown in Fig. 6, where enantioselectivity is plotted versus conversion. This plot makes the striking observation that the parameter linked to enantioselectivity in all of these diverse cases is *conversion* of substrate.

This observation appears all the more intriguing when it is considered that conversion of substrate is independent of kinetic variables such as reaction time or number of catalyst turnovers

which vary significantly over the wide range of conditions employed. Figs. 6 and 7 serve to highlight this conclusion. Enantioselectivity reached its plateau at an *identical conversion level* for a fifty-fold difference in reaction times (Fig. 6 shows this result for a 60 K range of reaction temperature), as well as for a four-fold difference in the number of turnovers per catalyst site (Fig. 7 shows this result for different initial substrate concentrations). Neither pretreatment of the catalyst, nor pretreatment or concentration level of the modifier, nor even the type of solvent employed, could alter this link between rising enantioselectivity and conversion of substrate. Rate behavior also followed this trend, giving a peak at near 20% conversion under all of the conditions given in Table 1.

Together these results suggest that the progression of the hydrogenation reaction itself is the key to achieving the steady-state enantioselectivity. It appears that a reaction-induced modification of the surface, requiring a specific ratio of reactants and products, and perhaps intermediate species, appears to be necessary to construct the sites which give the ultimate enantioselective performance. This leads to the conclusion that ex-situ characterization of the catalyst surface sites may be insufficient to provide a

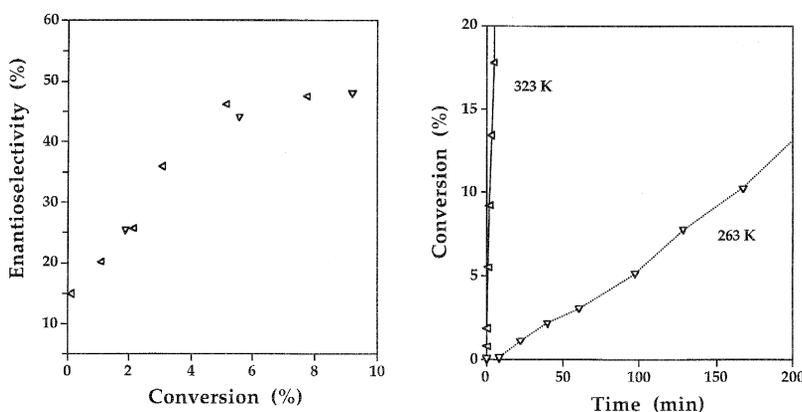


Fig. 7. Comparison of catalytic behavior at 263 K (∇) and 323 K (\triangleleft) in the hydrogenation of ethyl pyruvate using cinchona-modified Pt/Al₂O₃ at 580 kPa (see Table 1 for reaction conditions). (a) Enantiomeric excess as a function of conversion; (b) conversion as a function of reaction time.

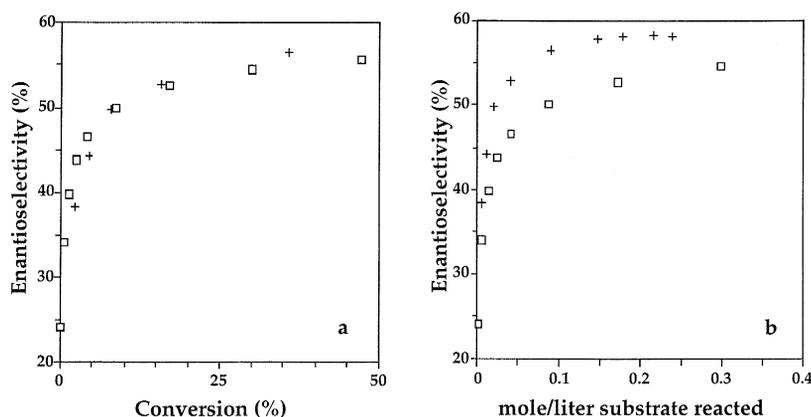


Fig. 8. Comparison of catalytic behavior for initial substrate concentrations of 1 M (□) and 0.25 M (+) in the hydrogenation of ethyl pyruvate using cinchonamodified Pt/Al₂O₃ at 580 kPa (see Table 1 for reaction conditions). (a) Enantiomeric excess as a function of conversion; (b) enantiomeric excess as a function of reaction time.

meaningful rationalization of the catalytic behavior of this system (Fig. 8).

4. Conclusions

Two examples from both homogeneous and heterogeneous asymmetric hydrogenation are presented to highlight the role that reaction dynamics may play in determining enantioselectivity. A complex network of series-parallel reactions was observed during the hydrogenation of geraniol using a Ru(*S*)-binap catalyst. The relative rates of various reactions in this hydrogenation-isomerization network was found to be a sensitive function of reaction conditions. The wide variation in enantioselectivity which may be observed for this system demonstrates that a general understanding of the reaction kinetics must accompany considerations of the stereochemical aspects of the chiral catalyst when interpreting the enantioselective efficiency of a catalyst system.

The phenomenon of a rising initial rate and increasing enantioselectivity in the reaction of α -keto esters using a cinchonidine-modified supported Pt catalyst was linked to *conversion* over a wide range of conditions. A reaction-driven equilibration of the chiral surface environment was proposed, underscoring the impor-

tance of considering reaction-induced changes in surface chemistry in an ultimate rationalization of the nature of active surface sites for asymmetric hydrogenation.

Acknowledgements

DEB would like to dedicate this paper to the memory of W.F. Bardey.

References

- [1] W.S. Knowles, Acc. Chem. Res. 16 (1983) 106; C.R. Landis and J. Halpern, J. Am. Chem. Soc. 109 (1987) 1746.
- [2] R. Noyori, Asymmetric Catalysis in Organic Synthesis (Wiley-Interscience, New York, 1994) ch. 5.
- [3] H.U. Blaser and A. Baiker, in: Handbook of Heterogeneous Catalysis, Eds. Ertl, Knozinger and Weitkamp, in press.
- [4] R. Noyori, Asymmetric Catalysis in Organic Synthesis (Wiley-Interscience, New York, 1994) pp. 2–3.
- [5] Y. Sun, J. Wang, C. LeBlond, J. Laquidara, J.R. Sowa, Jr. and D.G. Blackmond, J. Am. Chem. Soc. 117 (1995) 12647.
- [6] U.K. Singh, R.N. Landau, Y. Sun, C. LeBlond, D.G. Blackmond, S.K. Tanielyan and R.L. Augustine, J. Catal. 154 (1995) 91.
- [7] Y. Sun, J. Wang, C. LeBlond, R.N. Landau and D.G. Blackmond, J. Catal., 161 (1996) 752.
- [8] J. Wang, Y. Sun, C. LeBlond, R.N. Landau and D.G. Blackmond, J. Catal., 161 (1996) 759.
- [9] Y. Sun, R.N. Landau, J. Wang, C. LeBlond and D.G. Blackmond, J. Am. Chem. Soc. 118 (1996) 1348.
- [10] R.N. Landau, U.K. Singh, F.P. Gortsema, Y. Sun, D.G. Blackmond, S.C. Gomolka, T. Lam and M. Futran, J. Catal. 157 (1995) 201.

- [11] H. Takaya, T. Ohta, S.-I. Inoue, M. Tokunaga, M. Kitamura and R. Noyori, *Org. Synth.* 72 (1993) 74.
- [12] R. Reamer, unpublished data.
- [13] M. Garland and H.U. Blaser, *JACS* 112 (1990) 7048; H.U. Blaser, M. Garland and H.P. Jallet, *J. Catal.* 144 (1993) 569.
- [14] M. Garland, H.P. Jalett and H.U. Blaser, in: *Heterogeneous Catalysis and Fine Chemicals II*, Eds. M. Guisnet et al. (Elsevier Science Publishers, Amsterdam, 1991) p. 177.
- [15] I.M. Sutherland, A. Ibbotson, R.B. Moyes and P.B. Wells, *J. Catal.* 125 (1990) 77; P.A. Meheux, A. Ibbotson and P.B. Wells, *J. Catal.* 128 (1991) 387.